UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: September 14, 2022

SUBJECT: Risk Assessment for Dipropylene Glycol (tradename Honey Cake-TGAI) as an Aerosol Disinfectant

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This document provides the preliminary human health and ecological risk assessment conducted in support of the proposed new uses of dipropylene glycol as an air sanitizer for household and commercial use.

Introduction

Reckitt Benckiser, LLC has submitted a request for a new end-use product (EP), trademark Honey Cake® (EPA Reg. No. 777-RUG) containing the active ingredient (a.i.) dipropylene glycol. This product is intended to be used as an air sanitizer for household and commercial use.

During registration review, the dipropylene glycol case was merged with propylene glycol and triethylene glycol because of their similar use patterns, comparable chemical, physical, and environmental fate characteristics, low mammalian toxicity and low toxicity to non- target aquatic and terrestrial organisms (US EPA, 2013a). The available data from the merged cases is used to inform this risk assessment. Dipropylene glycol is currently registered for use as an aerosol deodorizer spray for use in commercial/institutional, food establishment, residential, and medical settings.

New Use Pattern

The proposed product contains 14% dipropylene glycol and is intended to be used as an aerosol sanitizer and deodorizer for use in commercial and residential settings. Within these settings the product can be used in rooms such as day care centers, kitchens, and patient rooms. Dipropylene glycol is currently registered for use as a deodorizing aerosol spray, which specifically targets bacteria. This product's new use is as sanitizing aerosol spray, which can kill viruses. The proposed label includes the following use directions to sanitize the air:

"**To kill Bacteria and Viruses † in the Air:** Shake well before each use. Close all doors, windows, and air vents. Hold can upright, (press button) and spray towards the center of room in a sweeping motion (back and forth) (left and right) for 30 seconds. Room size defined as (10ft x 10ft x 8ft) (800 cu ft.). After spraying (exit)(leave) room (for) (4 minutes for bacteria) (and) (12 minutes for viruses) (for duration of contact time), then resume normal room ventilation. Rinse food contact surfaces with potable water after use."

This spray can be used five times a day; each application is approximately 42 mg of product, 6 mg of a.i. The label does not indicate if the spray can be used daily or if the spray must be spaced out over the course of the day. The initial concentration after the spray and before ventilation is to resume will be 0.26 mg/m^3. Conservatively assuming the product is sprayed in back-to-back applications (i.e., no ventilation in between applications) and without settling, the maximum concentration in the air after 5 sprays would be 1.3 mg/m^3. This concentration would be expected to decrease based on ventilation rates of the room.

Human Health Risk Assessment

Based on the new air sanitization use, there is potential for oral (indirect food contact), dermal, inhalation, and incidental ingestion exposures to dipropylene glycol. However, a qualitative risk assessment was deemed appropriate for the proposed new use of dipropylene glycol because there is no evidence of adverse effects at doses up to the established limit dose in repeat – exposure oral (1000 mg/kg/day), dermal (1000 mg/kg/day) and inhalation (1 mg/L or 1000 mg/m^3) toxicity studies across the available data for triethylene glycol, propylene glycol or dipropylene glycol. Therefore, no toxicological endpoints of concern have been established based on review of the available mammalian toxicity data. Due to the low order of toxicity and low application rates from the proposed use of dipropylene glycol as an air sanitizer for household and commercial use, no risks of concern are anticipated for the potential routes of exposures (dietary, occupational, or residential).

Aggregate exposure

In examining aggregate exposure, the agency takes into account the available and reliable information concerning exposures to pesticide residues in food and drinking water, and non-occupational pesticide exposures. An aggregate risk assessment is not conducted because toxicological endpoints for propylene glycol, dipropylene glycol, and triethylene glycol have not been established (US EPA, 2013b).

Environmental

The agency does not anticipate the need to conduct an environmental risk assessment for the proposed use of dipropylene glycol because the indoor air sanitization application methods are not expected to result in exposure of terrestrial or aquatic organisms. In addition, the application via aerosol cans is not expected to result in down-the-drain disposal and there is no direct exposure to non-target organisms.

Conclusion

Although there is potential for oral, dermal and inhalation exposure to dipropylene glycol based on the proposed use pattern, no toxicological endpoints of concern were identified due to low toxicity across the available database. Therefore, a qualitative risk assessment was deemed appropriate, and no risks of concern were identified. No further risk assessment is needed at this time.

References

US EPA 2003. AD's Occupational and Residential Exposure Chapter for the Triethylene glycol Registration Eligibility Decision (RED) Document. (Case No. 3146). PC Code 083501. (Memorandum: T. Leighton, 9/26/03).

US EPA 2004. Propylene/ Dipropylene Glycol- Report of the Antimicrobials Division Toxicology Endpoint Selection Committee. (Memorandum: T. McMahon, June 20, 2004).

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US EPA 2005. Triethylene glycol: Revised Toxicology Chapter in Support of Issuance of the Registration Eligibility Decision (RED) Document. PC Code: 083501. Registration Case Number: 3146. DP#: 325786 (Memorandum: M. Centra, 10/11/2005).

US EPA 2006. Propylene/ Dipropylene Glycol Revised Ecological Hazard and Environmental Risk Characterization Chapter for the Registration Eligibility Decision (RED) Document. (Case No. 3146). PC Code 083501. (Memorandum: Kathryn Montague, February 14, 2006).

US EPA 2007. Propylene/ Dipropylene Glycol: AD's Risk Assessment for Issuance of the Registration Eligibility Decision (RED) Document. Reregistration Case No.: 3126. PC Codes: 068603, 068604. (Memorandum: S. Williams-Foy, February 5, 2007).

US EPA 2013a. Propylene glycol, Dipropylene glycol and Triethylene glycol Preliminary Work Plan. Registration Review: Initial Docket Case Numbers: 3126 and 3146. June 2013. Docket Numbers EPA-HQ-OPP-2013-0218 and EPA-HQ-OPP-2013-0219.

US EPA 2013b. Propylene glycol, Dipropylene glycol and Triethylene glycol Final Work Plan. Registration Review: Initial Docket Case Numbers: 3126 and 3146. December 2013. Docket Numbers EPA-HQ-OPP-2013-0218 and EPA-HQ-OPP-2013-0219.

APPENDIX A: Toxicology Profile

Dipropylene glycol

The dipropylene glycol (DiPG) toxicological database is comprised of studies submitted by the Glycols Joint Venture Consortium and published literature studies. The acute toxicity of DiPG is low by the oral, dermal, and inhalation routes of exposure. Toxicity Category IV is assigned for acute toxic effects of DiPG (Table 1). Acute oral LD_{50} values were greater than 5010 mg/kg/day when DiPG was administered to Sprague-Dawley male and female rats (MRID 43760801). When DiPG was administered topically to NZW rabbits, the dermal LD_{50} was also greater than 5010 mg/kg/day (highest dose tested).

In a 4-hour inhalation whole-body exposure study with Sprague-Dawley rats, the LC_{50} was found to be greater than 2.34 mg/L. There were no treatment-related effects observed in rats exposed to DiPG and all of the animals survived the exposure and observation period with no indication of toxicity (MRID 43760803).

Instillation of 0.1 mL DiPG in eyes of New Zealand White (NZW) rabbits showed no evidence of corneal damage, and DiPG was classified as a slight irritant based on observed conjunctival irritation that subsided within 24 hours (43760804). DiPG (0.5 mL of 100% TGAI) was administered to
NZW rabbits in a primary dermal irritation study. There was evidence of erythema in a single site that subsided in 24 hours while there were no traces of edema observed in treated animals; DiPG was classified as a non-irritant (MRID 43760805).

A study for dermal sensitization assessed a single challenge application of 0.5 mL DiPG (100% purity) to guinea pigs that had previously been treated with DiPG. The topical administration did not produce any evidence of dermal sensitization in treated animals (MRID 43760806).

In multiple open literature reports, when rats were exposed to DiPG by the oral route, the acute oral toxicity LD_{50}
values were similar to PG values and ranged from greater than 5000 to 15000 mg/kg/day for treated animals (MRID 46892504). DiPG was found to be an irritant to rabbits when administered in an undiluted dose of 510 mg in a primary eye irritation study (NIOSH, 1981).

Intraperitoneal and intravenous injections to rodents resulted in toxicity values similar to other acute studies, with LD_{50} values ranging from 4600-10000 and 5800-11500 mg/kg/day, respectively (Latven, 1939; Bartsch, 1976; Sax, 1979; Fischer, 1949; Weatherby, 1938; Budden, 1979).

Table 1. Acute Toxicity Profile of Dipropylene Glycol

Guideline	Study Type	MRID Number and/or Citation	Results	Toxicity Category
870.1100	Acute Oral - Rat	43760801	LD_{50} = > 5010 mg/kg	IV
870.1100	Acute Oral - Rat	46892504; NIOSH, 1981	LD_{50} > 5000-15000 mg/kg	IV
870.1200	Acute Dermal - Rabbit	43760802	LD_{50} = > 5010 mg/kg	IV
870.1300	Acute Inhalation - Rat	43760803	LC_{50}= > 2.34 mg/L	IV
870.2400	Acute Eye Irritation - Rabbit	43760804	Slight irritant	IV
870.2400	Acute Eye Irritation - Rabbit	NIOSH, 1981	Irritant	IV
870.2500	Acute Skin Irritation - Rabbit	43760805	Non irritant	IV
870.2600	Skin Sensitization - Guinea Pig	43760806	Non sensitizer	N/A

N/A = Not applicable

Propylene glycol

The toxicological database for propylene glycol (PG) is comprised of published literature studies (Table 2). Acute oral toxicity studies showed low acute toxicities with relatively high LD_{50} values (all considered to be Toxicity Category IV) ranging from 8000-46000 mg/kg/day PG for rodents and 18000-20000 mg/kg/day for both rabbits and guinea pigs. Signs of nervous system toxicity were reported in the rabbit and guinea pig but were at doses causing lethality. Similar nervous system effects (loss of balance, marked depression, and analgesia) were evident in one study with mice at LD_{50} values of 23000-24900 mg/kg/day (MRIDs 46892501; 46892509; Clark, 1979; Bartsch, 1976; Sax, 1979; Layton, 1987).

PG induced degeneration of goblet cells in the tracheal lining of rabbits after 20 and 120 minutes of aerosol exposure in an acute inhalation toxicity study; no other toxicological effects were observed (US EPA 2013b). In primary eye irritation studies, PG was instilled in the eyes of rabbits (0.1-0.5 mL). There were no treatment-related effects on the corneas of the animals and

PG was classified as a non-irritant (MRIDs 46892104; 46892502; 46892507; Clark, 1979; Draize, 1944; Guillot, 1982). Acute dermal toxicity studies were not available for PG. In a series of skin sensitization tests, no reactions were observed in guinea pigs exposed to solutions of PG up to 70% active ingredient (MRID 46892104).

Additionally, several studies established intraperitoneal and intravenous LD_{50} values for mice, rats, and rabbits. The acute LD_{50} values for intraperitoneal injection of PG ranged from 11200-13000 mg/kg/day for rodents. Similar, but lower, values were observed in intravenous injections experiments; with $LD5_0$ ranges of 6200-8000 mg/kg/day for rodents and 6500 mg/kg/day for rabbits (Latven, 1939; Bartsch, 1976; Sax, 1979; Fischer, 1949; Weatherby, 1938; Budden, 1979).

Table 2. Acute Toxicity Profile of Propylene Glycol

Guideline	Study Type	MRID Number and/or Citation	Results	Toxicity Category
870.1100	Acute Oral - Rat	46892501; 46892509; Clark, 1979; Bartsch, 1976; Sax, 1979; Layton, 1987	LD_{50} = 8000-46000 mg/kg	IV
870.1300	Acute Inhalation - Rat	Konradova, 1978	LC_{50} > 2.0 mg/L (no deaths)	IV
870.2400	Acute Eye Irritation - Rabbit	46892104; 46892502; 46892508; Clark, 1979; Draize, 1954; Guillot, 1982	Non irritant	IV
870.2500	Acute Skin Irritation - Rabbit	Clark, 1979	Non irritant	IV
870.2600	Skin Sensitization – Guinea pig	Kero, 1980	Non sensitizer	NA

N/A = Not applicable

Triethylene Glycol

Published literature studies submitted by the Glycols Joint Venture consortium for triethylene glycol (TEG) show low toxicity (Toxicity Categories III and IV) following acute exposures (Table 16). The acute oral and dermal toxicity of TEG appears to be low, with reported oral LD_{50} values ranging from 15-22 g/kg compiled from monographs and review articles. The data available on acute dermal toxicity were not sufficient to establish a dermal LD_{50}, but the data

requirement was waived based on the low order of toxicity observed in other studies with TEG. Data on inhalation toxicity showed a maximum tolerated level of 800 mg/m^3 in rats, but intratracheal instillation of 0.25 cc undiluted chemical caused marked pulmonary irritation, edema, and later, fibrosis and abcess formation in these animals (intratracheal instillation is not an accepted route of administration for the Agency's toxicity testing guidelines). Published literature data on the skin and eye irritation as well as skin sensitization showed TEG to be non-irritating to the skin and eye (when tested at the limit doses established by the Agency for acute toxicity testing) and not a dermal sensitizer (Safety Assessment of Triethylene Glycol and PEG-4, 2003; Budavari, 1989; Clayton, 1981-1982; Smyth, 1941).

TEG was evaluated for acute inhalation toxicity in male and female Sprague- Dawley albino rats in a study submitted to the Agency's Office of Prevention, Pesticides, Toxic Substances, the former name of Office of Chemical Safety and Pollution Prevention (OCSPP). A review of this study by the Agency established a four-hour LC_{50} greater than 5.2 mg/L and places acute inhalation in Toxicity Category IV. Based on these results, this study is considered adequate for regulatory purposes, and it now replaces the earlier submitted acute inhalation information (Nachreiner, 1991).

Table 3. Acute Toxicity Profile of Triethylene Glycol

Guideline	Study Type	MRID Number and/or Citation	Results	Toxicity Category
870.1100	Acute Oral - Rat	42814404	LD_{50} = 15-22 g/kg	IV
870.1200	Acute Dermal - Rabbit	42814404	LD_{50} not determined	Study Requirement Waived
870.1300	Acute Inhalation - Rat	Nachreiner, 1991	LC_{50} > 5.2 mg/L	IV
870.2400	Acute Eye Irritation - Rat	42814404	Mild irritant	III
870.2500	Acute Skin Irritation - Rabbit	42814404	Slight irritant	IV
870.2600	Skin Sensitization	42814404	Son- sensitizer	N/A

Subchronic Toxicity

Propylene glycol

Subchronic toxicity studies for PG were available from published open literature studies. In a 15-week feeding study, there were no adverse toxicological effects observed in rats administered 2500 mg/kg/day PG in the diet (MRID 46892504). In another subchronic toxicity study, PG was administered to rats in drinking water for 140 days. Although there were clinical signs (CNS depression and minor liver toxicity) exhibited in animals at a dose of 13200 mg/kg/day, these effects occurred well above the testing limit dose of 1000 mg/kg/day established for an oral subchronic toxicity study in rats (Seindenfeld, 1932).

In a 90-day inhalation study, female rats were exposed to PG vapors (1.0 or 2.2 mg/L) for 6 hours/day, 5 days/week over a period of 90 days. Animals experienced decreases in body weight and food consumption, although there were no changes in respiratory rates, minute volumes, or tidal volumes during exposure. With the exception of a significant increase in the number of goblet cells in the nasal passages of the mid- and high-dose animals (both male and female) males were unaffected by PG treatment (0.16, 1.0, or 2.2 mg/L) in this subchronic inhalation study (MRID 46892103).

Dipropylene glycol

Two published literature studies were available to address the subchronic toxicity of DiPG. In a drinking water study, DiPG was administered to mice at concentrations of 715, 1350, 2620, 4790, or 11000 mg/kg/day for males and 1230, 2140, 4020, 7430, or 14700 mg/kg/day for females over a period of 90 days. There were treatment-related increases in mortality at the high dose for both males and females and increased body weight in females treated with 2140 mg/kg/day DiPG. (MRID 46892101).

In a similar study, male and female rats exhibited reductions in body weight at 425 and 1690 mg/kg/day, respectively, when exposed to DiPG in drinking water for 90 days (425, 890, 1840, 3890, or 12800 mg/kg/day for males and 460, 920, 1690, 3340, or 8950 mg/kg/day for females). Water consumption increased at the high-dose for all animals by the second week and continued throughout the remainder of the study. There were increases in weight and the appearance of lesions in liver and kidneys of treated animals at concentrations exceeding those that induced body weight reductions. High-dose (12800 mg/kg/day) males experienced testicular effects, hypoactivity and poor hair coats (MRID 46892208).

Triethylene Glycol

Repeat oral dosing studies conducted in rats showed, in general, that the chemical was either without any adverse effects or produced toxicities only at doses at or greater than the limit doses established for EPA guideline test requirements. TEG administered in the drinking water to rats at concentrations of 3% and 5% by volume for 30 days showed signs of toxicity (weight loss,

alopecia and poor grooming) at the lower concentration with one animal dying on day 25 of the study. All rats in the 3% test group survived to study completion with no signs of toxicities (Lauter, 1940). In a 14-day oral toxicity study, Fischer 344 rats receiving TEG in the feed (doses equivalent to 1132, 2311, or 3916 mg/kg/day for males and 1177, 2411, or 6209 mg/kg/day for females) showed only changes in urinalysis (increased urine volume, decreased urine pH, and decreased urine triple phosphate crystals) at the highest respective doses tested in male and female rats (Union Carbide, 1989). In a third oral toxicity study conducted for 90-days in rats, TEG was administered in the diet at doses of 748, 1522 or 3849 mg/kg/day (males) and 848, 1699, or 4360 mg/kg (females). Although toxicities were noted at the high dose in male and female rats (decreases in body weight, slight decreases in hemoglobin and hematocrit, slight increases in mean corpuscular volume, and increased relative kidney and brain weights), these effects were noted at dose levels that exceed the established limit dose of 1000 mg/kg/day for such studies Union Carbide, 1990).

In a 21-day dermal toxicity study, there was no evidence of dermal or systemic toxicity from repeated dermal applications of 2 ml (approximately 600 mg/kg) TEG applied to the skin of rabbits (Guillot, 1982). These results are supported by TEGs' low dermal irritancy a negative response as a skin sensitizer (MRID 42814404).

Sprague-Dawley rats exposed (whole body) to TEG in an aerosol inhalation study at concentrations of 494, 2011, or 4842 mg/m3 (0.5, 2.0, or 5.0 mg/L/day), for six hours a day, nine times over a two-week period showed the following toxicities at the highest concentration level tested: ataxia, prostration, unkept fur, labored respiration (males only), ocular discharge, swollen periocular tissue, perinasal and perioral encrustation, blepharospasm and reduced body weight. Necropies revealed hyperinflation of the lungs, ocular opacity, congestion and hemorrhage in many organs and tissues (pituitary gland, brain, nasal mucosa, kidney, thymus and lungs). All high-dose group rats died or were sacrificed moribund by day 5 of the study. Clinical signs of toxicity observed at the low- and mid-dose of 0.5 and 2.0 mg/L/day, respectively, were limited to swollen periocular tissues and perinasal encrustations. Treatment-related changes in organ weights in mid-dose males included an increase in liver and kidney weights relative to body weight; mid-dose females showed increases in absolute and relative (to body and brain weights) liver and kidney weights. Statistically significant clinical chemistry findings for males treated with 2.0 mg/L/day TEG included an increase in ALT activity and a decrease in serum creatinine levels. Mid-dose females showed increases in urea nitrogen, inorganic phosphorus, ALT and ALK activity, and decreases in glucose, creatinine, and chloride. However, the changes in organ weights and clinical chemistry findings were not correlated with any histopathological observations (Sun, 1992).

Rats exposed to the test material via a whole-body inhalation protocol could also be exposed to TEG via the oral and dermal routes. These additional routes of exposure may have increased the total dose received and contributed to the toxicities observed in the whole-body exposure inhalation study. Therefore, a second study was conducted using a nose-only exposure for 6 hours a day, 9 consecutive days. In this second inhalation toxicity study, mean exposure concentrations of 102, 517, or 1036 mg/m3 (approximately 0.1, 0.5, 1.0 mg/L/day) TEG produced no treatment-related toxicities at any dose tested (Norris, 1994). Monkeys exposed by inhalation to approximately 1 ppm vapor from two weeks to 13 months and human volunteers

exposed to air saturated with vapor (approximately 0.5 to 1 ppm) showed no adverse reactions or histopathological changes suggestive of toxicity from prolonged exposure to TEG (Robertson, 1947).

Dogs given daily intravenous injections (0.1 or 0.5 ml/kg) of TEG for four weeks showed no mortality or toxicity with the exception of flattened epithelial cells in the urine and phlebitis at the site of injection (Stenger, 1968).

Developmental and Reproductive Toxicity

Open literature studies examining the developmental and reproductive toxicity of propylene/dipropylene/TEG showed minimal evidence of toxicity at relatively high concentrations (10,000 mg/kg/day) that exceed the established limit dose of 1000 mg/kg/day.

Propylene glycol

PG, administered to mice at a concentration of 10,000 mg/kg/day in drinking water, did not produce any overt adverse effects in fetal development (MRID 46892201). In a second study, PG administered to mice via subcutaneous injections at a dose of 10,400 mg/kg/day on gestation day (GD) 9, 10, and 11 did not exhibit significant increases in fetal malformations (MRID 46892203). Two additional studies involving oral administration of PG in mice up to concentrations of 10,400 mg/kg/day did not induce any maternal, reproductive, or developmental toxicity in this study (MRID 46892508; Driscoll, 1993).

Several developmental studies were performed on rats, mice, rabbits, and hamsters in which oral doses of PG that ranged from 12.3-1600 mg/kg/day were administered during gestation. In all four studies, there were no incidents of treatment-related maternal, reproductive, or developmental toxicities observed in this study (MRID 46892207; FDRL, 1973; NTP, 1973). PG was administered to rats (1600-6200 mg/kg/day), mice (1550-10,000 mg/kg/day), and rabbits (1230 mg/kg/day) during gestation via a stomach tube. There were no adverse reproductive effects observed in any of these experiments. However, a slight maternal toxicity was noted in mice treated with 10,000 mg/kg/day PG (highest dose administered) on GD 8-12 (MRID 46892508; FDRL, 1973).

In a second reproductive toxicity study, rats from three successive generations were orally administered 2.5, 5, 7.5, 10, 20, or 30% PG. No adverse effects were observed up to the 20% dose (equivalent to a dietary level of approximately 11,900 mg/kg/day), where 50% of the animals failed to produce offspring. No offspring were produced by any of the rats in the 30% high-dose PG group (Guerrant, 1947).

Mice were administered 1820, 4800, or 10,100 mg/kg/day in drinking water over a course of 18 weeks in a third reproductive toxicity study. There were no treatment-related maternal, reproductive, or offspring effects observed at any of the PG doses tested in this study (MRID 46892204).

Dipropylene glycol

DiPG was administered to NZW rabbits in a developmental toxicity study at doses 0, 200, 400, 800 and 1200 mg/kg/day on GD 6-19. No treatment-related maternal, reproductive, or developmental toxicities were observed in treated animals (MRID 46892205). However, there were decreases in maternal food consumption and body weight in rats treated with 2000 and 5000 mg/kg/day DiPG. Increases in liver weight were also observed in these dose groups. No reproductive or developmental toxicity effects were observed in rats at any dose levels of DiPG from 800-5000 mg/kg/day (MRID 46892206).

Triethylene glycol

TEG was administered orally at doses of 0, 0.5, 5.6, and 11.27 g/kg/day in timed pregnant CD-1 mice from gestation Days 6 through 15. There were no treatment related maternal deaths and no abortions. Hyperactivity and rapid respiration were observed at the highest dose level tested. No effects were observed on maternal weight gain or food consumption at any dose level. Pregnancy outcome was unaffected at any dose level tested. There were no treatment-related effects observed for external or visceral malformations in offspring. Some evidence of delayed ossification was observed at the high dose level (Union Carbide, 1990).

In a second study, pregnant Sprague-Dawley rats were administered TEG by gavage on gestation days 6 through 15 at dose levels of 0, 1.0, 5.6, and 11.27 g/kg/day. There were no effects on maternal mortality and there were no abortions. Clinical toxicity was observed in maternal rats at the high dose and consisted of audible respiration, periocular encrustation, and perioral wetness. Decreased body weight and food consumption were observed in maternal rats at the 5.6 g/kg/day dose. No effects were observed at the 1.0 g/kg/day dose. In offspring, mean fetal body weight was decreased at the 11.27 g/kg/day dose level, but there were no treatment- related increases in external, visceral, or skeletal malformations Union Carbide, 1991). Published literature examined the effect of TEG on reproduction in Swiss CD-1 mice. Doses of 0, 0.3, 1.5, and 3% were administered in drinking water using a continuous breeding protocol. No effects on reproductive function were observed at any dose level tested (up to the high dose of 6.78 g/kg) including sperm concentration, morphology, and motility. Reduced pup weight was observed at the 1.5 and 3% doses of TEG (Bossert, 1992; Lamb, 1997).

In a study submitted to the Agency, rats were exposed to an atmosphere saturated with TEG (approx. 1 ppm) for 12-18 months with no adverse reproductive effects noted (Robertson, 1947; Goldstein, 1970).

The available developmental and reproductive studies conducted with TEG are from published sources or from studies submitted to the Office of Prevention, Pesticides, Toxic Substances, the former name of OCSPP and do not report all the data that are normally reported under the OPPTS 870 toxicity test guidelines. However, it is apparent that the toxicities observed in these studies are consistently manifested only at doses of TEG that exceed the established limit doses for animal studies and are of a non-specific nature. Therefore, there is no concern for the developmental or reproductive toxicity of TEG.

Chronic Toxicity and Carcinogenicity

Published literature studies examining the chronic toxicity and carcinogenic potential of propylene/dipropylene/TEG have shown the chemicals to be noncarcinogenic in rodent and non-rodent species under the conditions of each study. In addition, systemic adverse effects were noted only at doses of propylene, dipropylene, and TEG that exceed the limit dose of 1000 mg/kg/day established for mammalian chronic toxicity studies.

Propylene glycol

Several studies in the rat involving dietary, drinking water, and inhalation exposure to PG comprise the chronic toxicity database. There was little evidence of adverse toxicological effects at the relatively high concentrations used within these studies and chronic toxicity associated with PG was low. With the exception of slight liver damage in treated animals, there were no signs of toxic effects when PG was administered at 1230 or 2450 mg/kg/day in the diet for 2 years (Morris, 1942). In another study, slight liver damage and no other effects were observed in a 2- year drinking water study that administered 1834 mg/kg/day PG to rats (MRID 46892509; Braun, 1936).

In a continuous-exposure inhalation study, rats were exposed to 0.17-0.35 mg/L PG for 18 months and a chronic toxicity lowest observed adverse effect level (LOAEL) of 0.35 mg/L was established based on a 50% increase in body weight. There were no other effects observed in treated animals in this study (Robertson, 1947).

A carcinogenicity study in rats fed PG at dietary concentrations of 200, 400, 900, or 1700 mg/kg/day for males and 300, 500, 1000, or 2100 mg/kg/day for females was carried out for 2 years with little evidence of chronic toxicity or significant treatment-related neoplasms (46892504). In a dermal carcinogenicity study conducted in mice, there was no change in longevity or increase in tumors following chronic treatment with 0.02 mL of 10, 50 or 100% (MRID 46892301).

Dipropylene glycol

There were decreases in survival and body weight of male and female rats treated with 3040 and 2330 mg/kg/day DiPG, respectively, in drinking water for 2 years. Clinical signs of toxicity were noted in males with an increase in focal histiocytic and focal granulomatous inflammation in the liver. There was no evidence of carcinogenic activity in rats treated with DiPG over the course of 24 months (NTP, 2003e). In a similar mouse study, animals experienced decreased survival and body weight at the high-dose (2390 mg/kg/day for males and 1950 mg/kg/day for females) of DiPG tested in the study. Males in the 2390 mg/kg/day dose group also exhibited reduced water consumption. After 2 years of DiPG administration in drinking water, mice failed to show any evidence of carcinogenic activity (NTP, 2003d).

Triethylene glycol

Published literature sources examining the chronic toxicity and carcinogenic potential of TEG have shown the chemical to be non-toxic/negative in rodent species. In a 12-month study, monkeys receiving TEG (0.25 mL to 0.5 mL) orally in eggnog (approximately 50 to 100 times the quantity an animal could absorb by breathing glycol saturated air) showed no adverse effects in physiological function or organ histopathology (Robertson, 1947).

TEG administered in feed at levels of 0, 1, 2 or 4% to Osborn-Mendel rats for 2 years showed that the body weight gains, hematological parameters and clinical chemistries were not affected by treatment. Under the conditions of this study, TEG was not carcinogenic in rats. The doses tested in rats are equivalent to as much as 3 to 4 g/kg/day, which are well above the upper limit dose of 1 g/kg/day (1000 mg/kg/day) for testing pesticides via the oral route in subchronic and chronic toxicity studies (Fitzhugh, 1946).

Mutagenicity

Open published literature studies comprise the mutagenicity database for propylene/dipropylene glycol/TEG. In a battery of studies, propylene and DiPG did not exhibit mutagenic or genotoxic activity.

Propylene glycol

There were no signs of mutagenicity in several bacterial reverse mutation tests in tester strains TA 1535, TA 1537, TA 100, TA 98, and TA 1538 that were performed with concentrations of PG ranging from 1-10,000 µg/plate. PG did not induce mutant colonies and was negative in all cases (MRID 46892102; 46892503; Clark, 1979). Similar negative results were observed in additional mutagenicity studies, including an *in vitro* mammalian cell gene mutation test, an *in vitro* mammalian chromosome aberration test, a mammalian erythrocyte micronucleus test, and a dominant lethal assay (MRID 46892506; Litton Bionetics, 1974; Swenberg, 1976).

Dipropylene glycol

Non-mutagenic results were observed in both a bacterial reverse mutation and *in vitro* mammalian cell gene mutation test. There was no increase in mutant frequencies when DiPG was administered (100-10,000 µg/plate) to the bacterial tester strains TA 98, TA 100, TA 1535, and TA 1537 (NCI, 1986). In an *in vitro* mammalian cell gene mutation test, mice were given 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, 10, or 50 µL/mL DiPG and failed to produce a positive response in either the presence or absence of metabolic activation (NCI, 1987).

Triethylene glycol

TEG was tested for mutagenic or genotoxic potential and found to be negative in a battery of studies: a bacterial gene mutation assay using *Salmonela typhimurium*, an *in vitro* Chinese hamster ovary (CHO) mutation assay, an *in vitro* Chinese hamster ovary (CHO) chromosomal

aberration assay and an *in vitro* sister chromatid exchange assay (Guzzie, 1986a; Guzzie, 1986b; Slensinski, 1986a; Slensinski, 1986b).

Neurotoxicity

From the available toxicity studies, evidence of neurotoxicity was observed in mice, rabbits, and guinea pigs following a single dose of PG; loss of balance, marked depression, and analgesia observed at lethal doses of 18,400-24,900 mg/kg/day (Braun, 1936; Laug, 1939; Smyth, 1941; Latven, 1939). Central nervous system (CNS) depression was also noted in rats administered PG at greater than 13,200 mg/kg/day in drinking water for 140 days (Seidenfeld, 1932). However, these CNS effects were observed only at a dose level that far exceeds the established limit dose (1000 mg/kg/day) for an oral subchronic toxicity study. Based on a weight-of-evidence evaluation of the available data, the Agency does not anticipate needing neurotoxicity testing, including a developmental neurotoxicity study for either propylene or DiPG.

Metabolism and Excretion

Propylene glycol

In an elimination and metabolism study a maximum concentration of 29.21 ± 2.92 mmol/L PG was found in the blood of rats 2 hours with the high-dose administration of PG (treatment with 4.83, 9.66, 19.32, 38.64, and 77.28 mmol/kg PG) (Morshed, 1988). PG was readily absorbed in the gastrointestinal tract of several animals in other studies. The absorption was rapid and complete, and PG was broken down into glycogen (Hanzlik, 1939; Opitz, 1958; Salter, 1935; Van Winkle, 1941). PG was administered orally to humans (70 g) and dogs (150 g) in a NTIS study in which a portion of PG was metabolized, and an appreciable fraction was excreted in the urine. Within 10 hours, 20-25% of the 70 g dose given to the human subjects was excreted. The dogs excreted 20% of the 150 g dose within 24 hours (Hanzlik, 1939).

Dipropylene glycol

No metabolism studies conducted with DiPG are available in the toxicity data base.

Triethylene glycol

The fate of 14C-labeled TEG in rats and of unlabeled material in rabbits was studied. Following oral dosing, the rat and rabbit excreted most of the TEG in both unchanged and/or oxidized forms (mono- and dicarboxylic acid derivatives of TEG). In rabbits dosed with 200 or 2000 mg/kg TEG respectively excreted 34.3% or 28%, of the administered dose in the urine as unchanged TEG and 35.2% as a hydroxyacid form of this chemical. In the studies with rats, little if any C14-oxalate or C14- TEG in conjugated form was found in the urine. Trace amounts of orally administered 14C TEG were excreted in expired air as carbon dioxide (<1%) and in detectable amounts in feces (2 to 5 %). The total elimination of radioactivity (urine, feces and CO2) during the five-day period following an oral dose of labeled compound (22.5 mg) ranged from 91 to 98%. The majority of the radioactivity appeared in the urine (McKennis, 1962).

Dermal Absorption

Propylene glycol

There have been no reports dealing with PG and skin absorption. PG has been found to penetrate the outermost layer of the epidermis; however, because of this property, PG is commonly used as a cosmetic ingredient in many products. Although absorption through the skin is possible, it is doubtful any appreciable systemic/dermal injury would occur based on the lack of irritation in acute dermal studies, no evidence of chronic toxicity or tumor response following a 2-year dermal application study, and the widespread use in cosmetics that is considered safe (MRID 46892301; Clark, 1979).

Dipropylene glycol

No dermal penetration/skin absorption studies were identified for DiPG. Similar to PG, DiPG is used in many cosmetic formulations and has been generally recognized as a low toxicity chemical by the FDA. Dermal and systemic injury from skin exposure to DiPG is unlikely considering its widespread use in cosmetics, the lack of evidence of dermal toxicity in acute studies, and the lack of evidence of skin sensitization in repeat-exposure studies (MRIDs 43760802; 43760805; 43760806).

Triethylene glycol

No studies have been reported dealing with the skin absorption of TEG. Although it is possible that, under conditions of very severe prolonged exposures to this chemical, absorption through the skin may occur, it is doubtful any appreciable systemic/dermal injury would occur because TEG has (1) a low order of dermal irritancy (MRID 42814404), (2) is not a skin sensitizer (MRID 42814404) and (3) showed no evidence of dermal or systemic toxicity following repeated dermal applications of 2 ml (approximately 600 mg/kg) TEG applied to the skin of rabbits in a 21-day dermal toxicity study (Guillot, 1982).

Immunotoxicity

An immunotoxicity study is a data requirement for all antimicrobial pesticide chemicals under 40 CFR Part 158W, Data Requirements for Antimicrobial Pesticides. However, based on a weight of evidence approach, the agency concluded that immunotoxicity studies are not required for the Triethylene glycol, Propylene Glycol, Dipropylene Glycol Registration Review case. There were no adverse effects, including indicators of potential immunotoxicity, at doses of TEG, PG or DiPG up to the established limit dose (1,000 mg/kg/day) in the repeated dose toxicity studies. Consequently, the Agency identified these glycols as low toxicity chemicals with no human health toxicological endpoints of concern and conducted qualitative assessments. In addition, TEG, PG and DiPG are alcohols that do not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Furthermore, an Office of Pesticide Programs' retrospective analysis (2012) of the impact of the immunotoxicity study on human health risk assessments concluded that in no case (171 studies

on 155 chemicals) was the immunotoxicity POD (Point of Departure)/NOAELs (No-Observed-Adverse-Effects-Levels) the most sensitive toxicity endpoint of concern when compared to other existing toxicity endpoints in each respective chemical data base. For TEG, PG and DiPG, the (1) lack of immunotoxicity findings at or greater than the testing limit dose for repeated dose studies, (2) absence of structure activity relationships with known immunotoxicant chemicals, and (3) findings demonstrating the lack of impact of immunotoxicity studies on OPP human health risk assessments, a qualitative approach to assessing human health risks is appropriate for these glycols. Therefore, the Agency will not require an immunotoxicity study (OCSPP Test Guideline No. 870.7800) for risk assessment purposes.